

Non-invasive Ventilation Monitoring During Remifentanil Challenge in CyP450-Deficient Patient

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Introduction: When managing complicated patients, clinicians often need to push boundaries and experiment with intended use and/or dosing of medications. In order to minimize risk and improve patient outcome, unconventional therapies often rely on cutting edge monitoring technology. In this particular case we wanted to assess a patient's tolerance for remifentanil, specifically, monitoring her respiratory status without intubation or other airway manipulation. To accomplish this, along with conventional anesthesia equipment, we used a non-invasive impedance-based respiratory volume monitor (RVM) that provides real-time minute volume (MV) tidal volume (TV) and respiratory rate (RR) measurements.

Methods: A 50 y/o, 50 kg female patient with known CyP450 deficiency was enrolled in a remifentanil challenge trial to determine her tolerance for potential use of the drug during and after surgical procedures. Remifentanil's metabolic pathway suggested this would be successful. The trial was approved by the Brigham and Women's Hospital Desensitization Committee. The patient had successfully undergone seven (7) surgical procedures with Sevoflurane VIMA (Volatile Induction and Maintenance Anesthesia). Patient's CyP450 deficiency had disturbed her metabolism of conventional analgesics, and had led to complications and extended ICU hospitalization following conventional receipt of multi-drug anesthesia and postop care. For this trial, the patient was monitored in the ICU with a RVM (ExSpirom, Respiratory Motion, Waltham, MA), anesthesia machine (GE Aisys, GE Healthcare, Madison, WI) and multi-parameter physiological monitor (GE B850 multi-parameter monitor with integrated bispectral index (BIS), GE Healthcare, Madison, WI). Non-invasive MV, TV, RR were collected from the RVM. HR, BP, SpO₂, FiO₂, EtCO₂, and ETCO₂-based RR from the anesthesia machine via Salter nasal prongs (Salter Labs, Arvin, CA) with zero flow of supplemental oxygen throughout the trial, and BIS from the BIS monitor. For the challenge, 4 remifentanil bolus doses (1 mcg/ml concentration) were administered in ascending order (2 mcg, 5 mcg, 10 mcg, and 15 mcg) followed by a continuous infusion (0.05 mcg/kg/min x 30 min). Each subsequent dose was administered when the patient returned to baseline mentation, assessed by interactive conversation and BIS > 98. A first-order difference equation simulation was used to estimate the total remifentanil dose in the bloodstream, based on a remifentanil half-life of 4 min. Predicted MV (MV_{PRED}) was calculated based on patient's ideal body weight. Data and simulation were time-synched post-hoc and plotted on a time axis, zeroed at the time of the first bolus dose. All analyses were done in MATLAB 2014b (MathWorks, Framingham, MA).

Results: For the purposes of this case report we focus on the available respiratory variables (MV, TV, RR from RVM, EtCO₂ and RR from anesthesia machine) and mental status (from BIS monitor). The patient's baseline MV was 5.4 ± 1.0 L/min and MV_{PRED} was 5.2 L/min. RVM readings were continuously available throughout the study. The first administered bolus (2 mcg) resulted in no noticeable change in any of these variables (Fig 1A), except that EtCO₂ readings were found to be missing more than 60% of the time. The second bolus (5 mcg) triggered mild respiratory depression with a decrease in MV to ~80% MV_{pred}, coinciding with a transient dip in BIS down in the 91-92 range for approximately 3 minutes (Fig 1B). The respiratory depression was mostly due to a decrease in TV. Just as with the first dose, EtCO₂ failed to yield measurements over 40% of the time. With the 3rd & 4th boluses (10 & 15 mcg, respectively) we managed to sustain sedation (Fig 1C&D) for up-to 10-15 minutes with BIS measurements consistently in the 80-85 range. The RVM showed sustained respiratory depression at ~80% MV_{pred} during the same period, once again driven by a sustained decrease in TV and effectively no change in RR. With the patient sedated

and immobile, EtCO₂ readings were available more often, but showed no change from baseline until around minute 70, when the EtCO₂ abruptly decreased, despite patient's diminished ventilation. After a prolonged break to ensure all residual remifentanil was cleared, an infusion was initiated at 2.5 mcg/min, with a target steady-state dose of 15 mcg in the bloodstream. Sedation began within 11 minutes (BIS was below 80), as the amount of remifentanil in the bloodstream plateaued at approximately 13 mcg and MV once again settled at approximately 80% MV_{PRED}. A transient episode of partial wakefulness was noted around minute 124 (18 minutes after the start of the infusion), which resulted in a rapid increase of BIS and RMV measurements, and fall in EtCO₂. Continuing the infusion restored the sedative state. The patient recovered back to baseline wakefulness approximately 25 minutes after the infusion was discontinued. The patient was assessed as able to respond normally to remifentanil.

Conclusions: A continuous respiratory volume monitor can be used to measure minute volume, tidal volume and respiratory rate during drug trials without the need for patient intubation or other airway manipulation. Respiratory volume and rate parameters can be monitored successfully in the absence of supplemental oxygen delivery and gas monitoring. Tolerance to potentially respiratory depressive doses of remifentanil can be defined and monitored effectively.

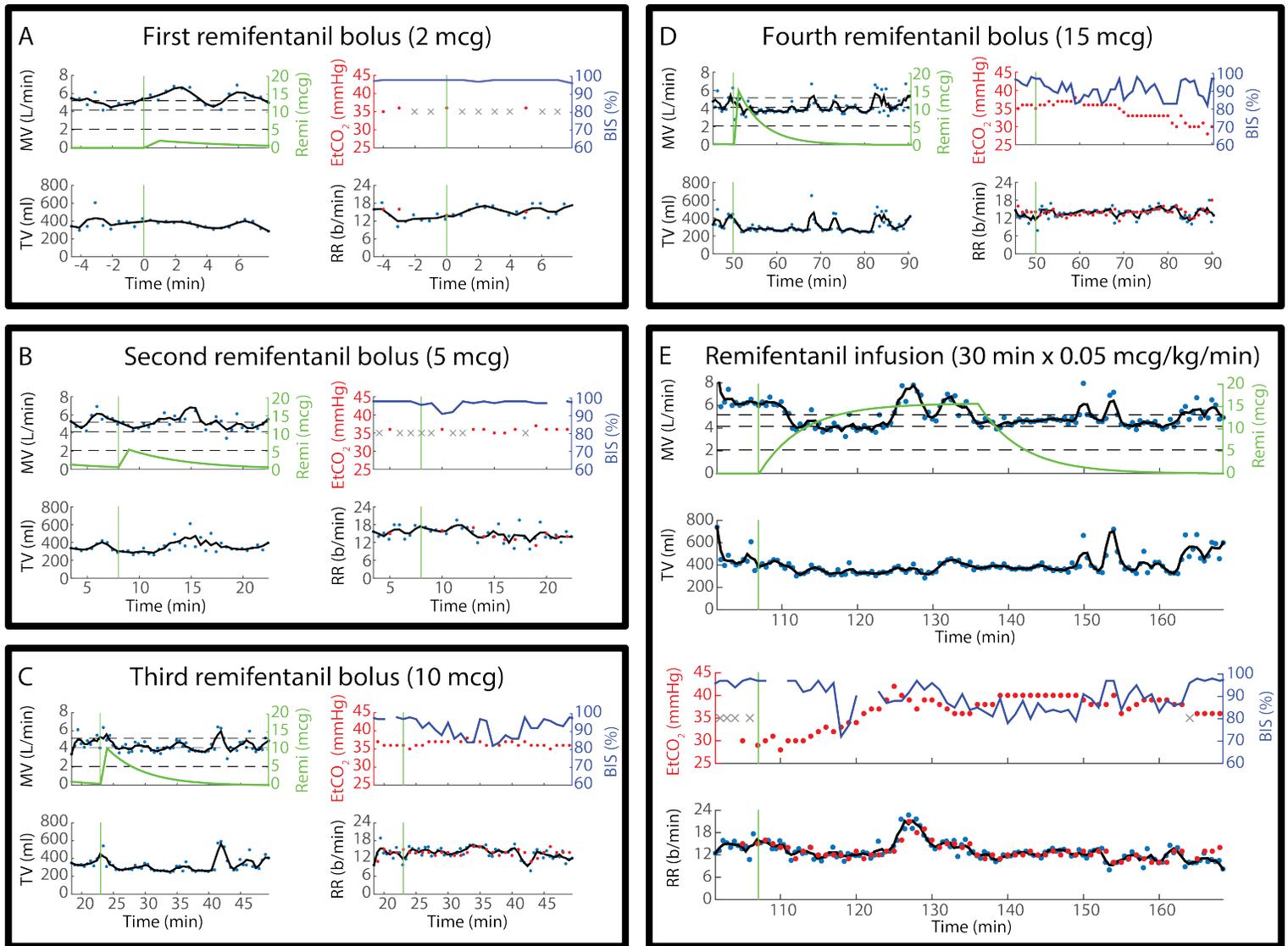


Figure 1: Time course of patient's vital signs during a remifentanyl challenge. Panels (A-D) depict the changes in monitored variables following individual bolus doses (2, 5, 10 and 15 mcg, respectively) and panel E depicts the effects of a 30-min infusion (0.05 mcg/kg/min or 2.5mcg/min). In each panel, the 4 sub-panels display the following monitored variables (from top-left in clockwise direction): (1) Minute Volume from RVM in black (left y-axis) and total remifentanyl in the bloodstream (green, right y-axis); (2) EtCO₂ (from nasal prongs measured by anesthesia machine) in black (left y-axis) and BIS index (from BIS monitor) in blue (right y-axis); (3) Respiratory Rate (from RVM) in blue with 2-minute average RR in black and RR from the anesthesia machine (from EtCO₂) in red; (4) Tidal Volume (from RVM) in blue and 2-minute average TV (black). In all EtCO₂ plots a gray X symbol at 35 mmHg indicates a missing EtCO₂ reading from the anesthesia machine. In the MV plots the horizontal black dashed lines represent 100%, 80% and 40% of the patient's MV_{PRED}. The patient's baseline MV during the 20 minutes before the trial was 5.4 ± 1.0 L/min, corresponding to 103 ± 19% predicted. All times are given as time since the first dose was administered.